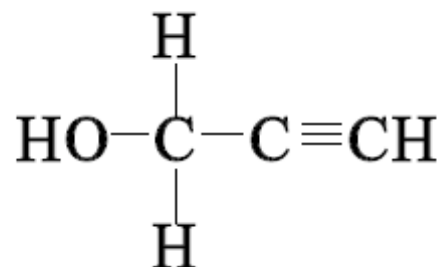




NTP
National Toxicology Program

Inhalation Studies of Propargyl Alcohol





Propargyl Alcohol

- Reactant/chemical intermediate
- Corrosion inhibitor
- Solvent stabilizer
- Polymer modifier

- Nominated by NCI
 - High production volume
 - Potential for human exposure in occupational settings

- *Salmonella* assay- positive in strain TA100 (-S9)
- Micronucleus assay- negative in males, equivocal in females



Results of 2-Week Studies in Rats and Mice

- Exposure Concentrations: 0, 31.3, 62.5, 125, 250, or 500 ppm
- Significant mortality
 - Male rats and mice, female mice: ≥ 125 ppm
 - Female rats: 250 or 500 ppm
- Mean body weights and body weight gains less than controls
 - Male rats and mice, female mice: 62.5 ppm
 - Female rats: 125 ppm
- Nonneoplastic lesions observed in the liver
 - Males and females: 250 or 500 ppm; male mice: 125 ppm
 - Moderate to marked periportal necrosis
 - Periportal congestion
 - Erythrophagocytosis



Results of 3-Month Studies in Rats

- Exposure Concentrations: 0, 4, 8, 16, 32, or 64 ppm
- Survival and mean body weights were similar to controls
- Nonneoplastic lesions were observed in the nose

Lesion	Sex	Exposure Concentration (ppm)					
		0	4	8	16	32	64
Respiratory Epithelium							
Hyperplasia	M	2	7*	5	7*	9**	10**
	F	0	2	4*	4*	10**	9**
Squamous Metaplasia	F	0	0	0	0	0	8**
Olfactory Epithelium							
Necrosis	M	0	0	0	0	2	5*
	F	0	0	0	0	3	5*

N=10; *P≤0.05; **P≤0.01



Results of 2-Year Studies in Rats

- Exposure Concentrations: 0, 16, 32, or 64 ppm
- Survival was decreased in males exposed to 32 and 64 ppm due to moribund sacrifices attributed to excessive lethargy
- Mean body weights were less than controls in males exposed to 64 ppm



Neoplastic Lesions in the 2-Year Studies in Male Rats

Lesion	Exposure Concentration (ppm)			
	0	16	32	64
Nose, Respiratory Epithelium				
Adenoma	0	0	0	3 ^a
All Organs				
Mononuclear Cell Leukemia	21	26	23	37 ^{**}

N=49-50

^aExceeded historical control incidence for 2-year inhalation studies: 1/447

^{**}P≤0.01



Nonneoplastic Lesions in the Nose of Rats

Lesion	Sex	Exposure Concentration (ppm)			
		0	16	32	64
Respiratory Epithelium					
Hyperplasia	M	5	21**	44**	42**
	F	2	23**	25**	36**
Glandular Hyperplasia	M	3	14**	39**	45**
	F	2	33**	44**	47**
Olfactory Epithelium					
Basal Cell Hyperplasia	M	0	19**	42**	42**
	F	0	28**	42**	48**
Atrophy	M	1	21**	26**	26**
	F	3	0	28**	37**
Respiratory Metaplasia	M	1	10**	18**	29**
	F	3	2	7	17**

N=49-50; **P≤0.01



Additional Nonneoplastic Lesions in the Nose

- Olfactory Epithelium
 - Hyperplasia
 - Glandular hyperplasia
 - Degeneration
 - Necrosis
 - Hyaline droplet accumulation
 - Chronic active inflammation

- Incidence was significantly increased in one or more exposed groups of male or female rats



Results of 3-Month Studies in Mice

- Exposure Concentrations: 0, 4, 8, 16, 32, or 64 ppm
- Survival was similar to controls
- Mean body weights were less than controls in males exposed to ≥ 8 ppm and females exposed to 32 and 64 ppm



Nonneoplastic Lesions in the Nose of Mice

- Males and Females exposed to 32 or 64 ppm
- Involved both the Respiratory and Olfactory Epithelium
- Lesions included:
 - Suppurative inflammation
 - Squamous metaplasia of the respiratory epithelium
 - Hyaline degeneration in the respiratory epithelium
 - Olfactory epithelial atrophy
 - Glandular hyperplasia in the olfactory region
 - Necrosis of olfactory epithelium
 - Turbinate atrophy



Results of 2-Year Studies in Mice

- Exposure Concentrations: 0, 8, 16, or 32 ppm
- Survival was similar to controls
- Mean body weights were less than controls in females exposed to 16 and 32 ppm



Neoplastic Lesions in the 2-Year Studies in Mice

Lesion	Sex	Exposure Concentration (ppm)			
		0	8	16	32
Nose, Respiratory Epithelium					
Adenoma ^a	M	0	1	4	7**
	F	0	2	4	6*
Harderian Gland					
Adenoma	M	3	10*	6	11*

N=49-50; *P≤0.05; **P≤0.01

^aNo respiratory epithelial adenomas reported in historical control mice

Males: inhalation 0/449; all routes 0/1,492

Females: inhalation 0/447; all routes 0/1,593



Nonneoplastic Lesions in the Nose of Male Mice

Lesion	Exposure Concentration (ppm)			
	0	8	16	32
Respiratory Epithelium				
Hyperplasia	1	49**	49**	50**
Glandular Hyperplasia	17	29*	40**	50**
Squamous Metaplasia	2	11*	36**	50**
Suppurative Inflammation	2	16**	25**	50**
Turbinate Atrophy	0	50**	49**	50**
Olfactory Epithelium				
Atrophy	0	3	21**	33**
Respiratory Metaplasia	5	0*	7	16*

N=49-50; *P≤0.05; **P≤0.01



Nonneoplastic Lesions of the Eye in Mice

Lesion	Sex	Exposure Concentration (ppm)			
		0	8	16	32
Cornea					
Chronic Active Inflammation	M	1	0	5	7*
	F	0	1	2	10**
Cataract	F	1	1	0	6*

N=48-50; *P≤0.05; **P≤0.01



Conclusions of the 2-Year Rat Studies

- *Some evidence of carcinogenic activity* of propargyl alcohol in male F344/N rats based on increased incidences of nasal respiratory epithelial adenoma and mononuclear cell leukemia.
- *No evidence of carcinogenic activity* of propargyl alcohol in female F344/N rats.
- Increased incidences of nonneoplastic lesions were observed in the nose.



Conclusions of the 2-Year Mouse Studies

- *Clear evidence of carcinogenic activity* of propargyl alcohol in male and female B6C3F1 mice based on increased incidences of nasal respiratory epithelial adenoma.
- Increased incidences of Harderian gland adenoma in male B6C3F1 mice may have been related to exposure.
- Increased incidences of nonneoplastic lesions were observed in the nose.